UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,448	11/07/2001	David Lewis	Mirus.030.03	3784

25032 7590 07/27/2005

MIRUS CORPORATION
505 SOUTH ROSA RD
MADISON, WI 53719

EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/007,448	LEWIS ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission mailed on December 23, 2004 has been entered.

Claim 1 has been amended.

Claims 1, 3-9, and 13-16 have been examined on the merits.

Response to Arguments

Applicants Amendment and Response filed December 23, 2004 has been considered. Rejections and/or objections not reiterated from the previous office action mailed November 23, 2004 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Applicants Amendments and Remarks filed February 24, 2005 and May 5, 2005 to comply with 37 CFR 1.121(c) are acknowledged.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-6, 8 and 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Kumasaka et al. (Journal of Clinical Investigation, 1996 Vol. 97:2362-2369).

Claim 1 is drawn to a process for delivering a naked polynucleotide into a cell of a mammal to inhibit protein expression comprising making the polynucleotide consisting of a sequence that is complementary to a nucleic acid sequence in the mammal, inserting the polynucleotide into a vessel in the mammal, wherein the vessel consists of arteries, arterioles, capillaries, venules, sinusoids, veins, lymphatics, and bile ducts, increasing the permeability of the vessel within the target tissue, and delivering the polynucleotide to the cell wherein the protein expression is inhibited. Claims 3-6 and 13-15 are dependent on claim 1 and include all the limitations of claim 1, with the further limitations, wherein vessel permeability is increased by increasing pressure against vessel walls by increasing a volume of fluid within the vessel, wherein the vessel is a tail

vein, wherein the cell is selected from a liver, spleen, heart, kidney, muscle or lung cells, and wherein the pressure increases extravascular volume.

Kumasaka et al. disclose a process for delivering a naked polynucleotide, ISIS 3082, into a cell of a mammal via intravenous injection. Kumasaka et al. disclose that ICAM-1 mRNA expression was detected and inhibited in the lung (see Figures 1 and 2). Kumasaka et al. disclose ISIS 3082 was injected into BALB/C mice through the tail vein and neutrophil emigration was detected in the lungs (see Figure 4).

It is noted that injection into the tail vein with ISIS 3082 is equivalent to increasing vessel permeability within the target tissue, by increasing pressure against vessel walls, increasing a volume of fluid within the vessel, and increasing extravascular volume as claimed because the method of intravascular injection would inherently increase pressure in the area of injection and at the point of injection. The pressure against the vessel walls would inherently be increased because the needle used is external to the tail vein. It is further noted that Kumasaka et al. are silent regarding the effects of ISIS 3082 on protein expression. However, given the inhibition of ICAM-1 mRNA expression by ISIS 3082, one of skill in the art would conclude that inhibition of protein expression would result to some degree, absent evidence to the contrary.

Therefore Kumasaka et al. anticipate claims 1, 3-6, and 13-15.

Response to Arguments

In response to this argument, Applicants argue that the claims have now been amended to indicate that increasing the permeability of the vessel is *within the target tissue*. Applicants contend that this is in contrast to Kumasaka et al. where the pressure is limited to the point of injection.

This argument has been fully considered, but is not found persuasive because the amendment to the claims to indicate that increasing the permeability of the vessel is *within the target tissue* does not obviate the instant rejection. Kumasaka et al. disclose a process for delivering a naked polynucleotide, ISIS 3082, into a cell of a mammal via intravenous tail vein injection. It is the Examiner's opinion that the injection method disclosed by Kumasaka et al. increases the permeability of the vessel within the tail vein (e.g. target tissue), since the needle used is external to the tail vein. Regardless of the fact that the pressure is limited to the point of injection as Applicants argue, the pressure is still within the target tissue (e.g. tail vein).

Therefore Kumasaka et al. anticipate claims 1, 3-6, and 13-15.

Claim 1, 3-6, 8, and 13-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Graham et al. (Journal of Pharmacology and Experimental Therapeutics, 1998 Vol. 286:447-458).

Claims 1, 3, 4, 5, 6, 8, and 13-15 are described above in the rejection anticipated by Kumasaka et al. Claim 16 is dependent on claim 1 and includes all the limitations of claim 1, with the further limitation wherein the vessel consists of liver.

Graham et al. disclose a process for delivering a naked polynucleotide, ISIS 1082, into a cell of a mammal via intravenous injection through the tail vein. Graham et al. disclose the metabolism, pharmacokinetics, and intraorgan distribution in tissues such as the liver (see Figures 2-5, 11, and 12).

It is noted that injection into the tail vein with ISIS 1082 is equivalent to increasing vessel permeability within the target tissue, by increasing pressure against vessel walls, increasing a volume of fluid within the vessel, and increasing extravascular volume as claimed because the method of intravascular injection would inherently increase pressure in the area of injection and at the point of injection. The pressure against the vessel walls would inherently be increased because the needle used is external to the tail vein. It is further noted that Graham et al. are silent regarding the effect of ISIS 1082 on protein expression. However, given the quantitative pharmacokinetic information provided by Graham et al. following intravenous administration of ISIS 1082, one of skill in the art would conclude that inhibition of protein expression would result to some degree, absent evidence to the contrary.

Therefore Graham et al. anticipate claims 1, 3-6, 8, and 13-16.

Response to Arguments

In response to this argument, Applicants argue that the claims have now been amended to indicate that the increasing the permeability of the vessel is *within the*

target tissue. Applicants contend that this is in contrast to Graham et al. where the pressure is limited to the point of injection.

This argument has been fully considered, but is not found persuasive because the amendment to the claims to indicate that the increasing the permeability of the vessel is *within the target tissue* does not obviate the instant rejection. Graham et al. disclose a process for delivering a naked polynucleotide, ISIS 1082, into a cell of a mammal via intravenous tail vein injection. It is the Examiner's opinion that the injection method disclosed by Graham et al. increases the permeability of the vessel within the tail vein (e.g. target tissue), since the needle used is external to the tail vein. Regardless of the fact that the pressure is limited to the point of injection as Applicants argue, the pressure is still within the target tissue (e.g. tail vein).

Therefore Graham et al. anticipate claims 1, 3-6, 8, and 13-16.

Claims 1, 3, 4, 5, 7, 9, and 13-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Kay et al. [U.S. Patent No. 6,107,027].

Claims 1, 3, 4, 5, 9, and 13-15 are described above in the rejection anticipated by Kumasaka et al. Claim 7 is dependent on claim 1 and includes all the limitations of claim 1 and provides the further limitation, wherein the vessel consists of a bile duct.

It is noted that the instant specification does not define the term "naked". However, the instant specification claims benefit of parent application USSN 09/450,315, filed November 29, 1999, now U.S. Patent No. 6,379,966. Referring to U.S. Patent No. 6,379,966 at column 3, lines 43-46, "the term naked nucleic acids

indicates that the nucleic acids are not associated with a transfection reagent or other delivery vehicle that is required for the nucleic acid to be delivered to a target cell".

Kay et al. disclose a method for inhibiting hepatitis C virus (HCV) RNA in cells comprising administering an adenovirus encoding a HCV ribozyme, which inhibits the hepatitis C virus (see claim 1). Kay et al. further disclose the adenovirus encoding a HCV ribozyme, which inhibits the hepatitis C virus RNA, is infused via the bile duct (see claim 7), inhibits hepatocyte cells (see claim 2), and inhibits hepatic mRNA expression in transgenic mice (see Figure 4B).

It is noted that injection into the bile duct with the adenovirus encoding a HCV ribozyme is equivalent to increasing vessel permeability within the target tissue, by increasing pressure against vessel walls, increasing a volume of fluid within the vessel, and increasing extravascular volume as claimed because the method of injection would inherently increase pressure in the area of injection and at the point of injection. The pressure against the vessel walls would inherently be increased because the needle used is external to the bile duct. It is further noted that Kay et al. are silent regarding the effect of the adenovirus encoding a HCV ribozyme on protein expression. However, given the inhibition of hepatic mRNA in transgenic mice by the adenovirus encoding a hepatitis C virus ribozyme, one of skill in the art would conclude that inhibition of protein expression would result to some degree, absent evidence to the contrary.

Therefore, Kay et al. anticipate claims 1, 3, 4, 5, 7, 9, and 13-15.

Response to Arguments

It is noted that a similar rejection was made of record in the Office Action mailed June 16, 2004. In the Office Action filed July 30, 2004, Applicants amended the claims, argued this rejection, and filed a §1.131 Declaration to establish invention for delivery of short polynucleotides prior to the effective date of the cited reference. In the subsequent Office Action mailed November 23, 2004, the Examiner withdrew the rejection in view of Applicants amendments to the claims and Applicants §1.131 Declaration. However, after careful reconsideration of the claims, the Examiner has found the §1.131 Declaration nonpersuasive in establishing invention for delivery of short polynucleotides prior to the effective date of the cited reference.

Claims 1, 3, 4, 5, 7, 9, and 13-15 are drawn to a process for delivering a naked polynucleotide into a cell of a mammal to inhibit protein expression. Kay et al. disclose a method for inhibiting hepatitis C virus RNA in cells comprising administering an adenovirus encoding a HCV ribozyme, which inhibits the hepatitis C virus RNA, wherein the ribozyme is infused via the bile duct (see claims 1 and 7). Applicant's §1.131 Declaration is largely directed to a method of inhibiting gene expression comprising administering a siRNA via high-pressure tail vein injection.

The first issue is that Kay et al. teach the delivery of a polynucleotide to the **bile duct** and Applicant's §1.131 Declaration shows results from experiments using only **tail vein injection**. The second issue is the Kay et al. patent was filed on September 11, 1995 and Applicants contend that the §1.131 Declaration establishes invention for delivery of short polynucleotides prior to the effective date of the cited reference. The

Examiner is assuming the short polynucleotides to be siRNA since the §1.131 Declaration is largely directed to the delivery of siRNA.

It is well known in the art that siRNA is a relatively new art. In fact, one of the earliest publications concerning delivery of double-stranded RNA (dsRNA) to inhibit target gene expression is that of Wianny and Zernicka-Goetz (Nature, 2000 Vol. 2:70-75). For example, Wianny and Zernicka-Goetz teach dsRNA-mediated inhibition of gene expression and RNAi offers new opportunities to study loss-of-function phenotypes in specific cells and at specific stages of development of the early mouse embryo.

In summary, in view of the fact that Kay et al. teach delivery of a naked polynucleotide to the bile duct and Applicant's §1.131 Declaration addresses only tail vein delivery, the §1.131 Declaration has not been found persuasive. Additionally, in view of the fact that the Kay patent was filed in 1995, and Applicant's §1.131 Declaration is largely directed to a method of inhibiting gene expression comprising delivery of siRNA, of which was not known until early 2001, the §1.131 Declaration has not been found persuasive.

Therefore, Kay et al. anticipate claims 1, 3, 4, 5, 7, 9, and 13-15.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
July 19, 2005

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600